

# The importance of heterocyclic compounds in anti-cancer drug design

Heterocycles are key structural components of many of the anti-cancer drugs available on the market today. Indeed, of the novel molecular anti-cancer agents approved by the FDA between 2010 and 2015, almost two-thirds contained heterocyclic rings within their structures. Their prevalence in anti-cancer drug design can be partly attributed to their being extremely common in nature, with a vast number of cellular processes and mechanisms having evolved the ability to interact with them. Their versatility means there are multiple metabolic pathways and cellular processes within cancer pathology that can be susceptible to heterocycle-based drugs. In this article, we look at some of the most important heterocyclic compounds currently implicated in cancer therapy, both on the market and in development, discuss the properties that make them valuable as anti-cancer drugs, and consider the benefits of including heterocycles within high-throughput screening libraries.

**By Simon Pearce**

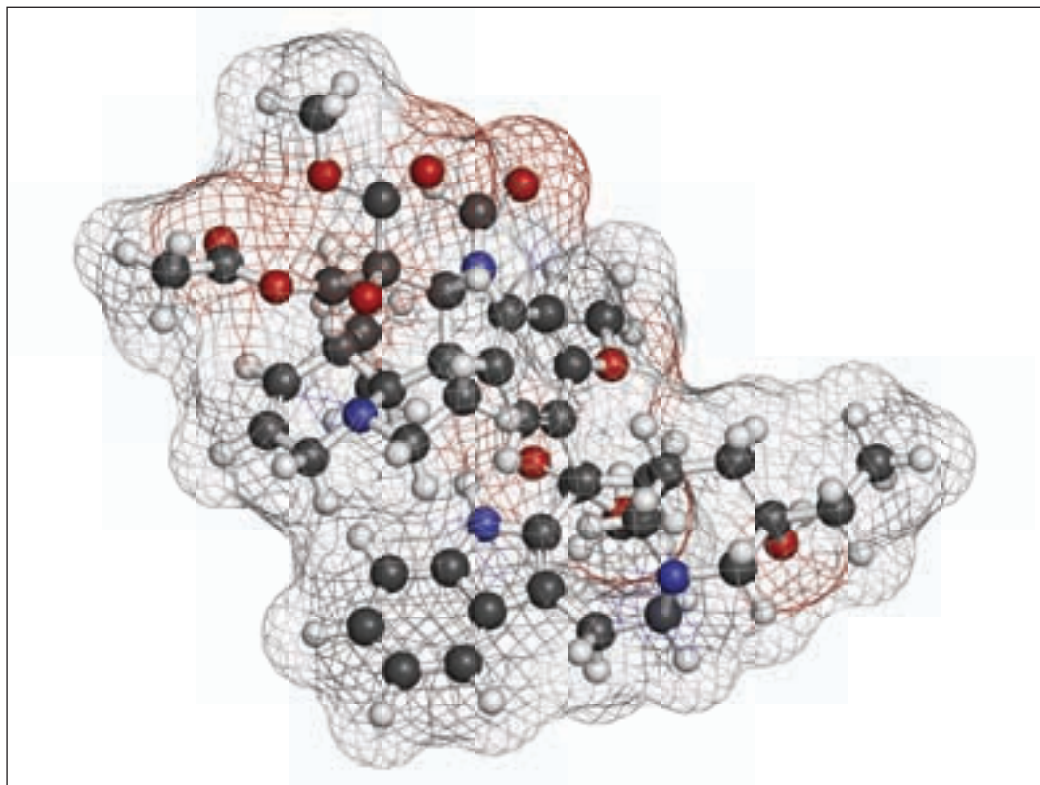
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**D**efined as cyclic compounds containing ring member atoms of carbon and at least one other element (such as nitrogen, oxygen and sulfur), heterocycles are common in biology, featuring in a wide range of structures from enzyme co-factors through to amino acids and proteins. They play a vital role in the metabolism of all living things, and are utilised at almost every stage of the many biochemical processes necessary to sustain life. Their prevalence is partly down to the broad range of interactions these structures are involved with, made possible due to the physico-chemical properties of their heteroatoms that can behave as either acids or bases, depending on the pH of their environment<sup>1</sup>.

The ability of heterocycles to engage in a wide

variety of intermolecular interactions, including hydrogen bond donor/acceptor capability, pi-stacking interactions, metal co-ordination bonds as well as van der Waals and hydrophobic forces, allows them to bind with enzymes in a multitude of ways. In addition, their wide range of ring sizes and structural permutations means heterocycles come in a broad range of shapes and sizes, allowing them to match the equally diverse structural range of enzyme binding pockets.

With their functional versatility, extremely common occurrence in nature, and involvement in large numbers of biological pathways, will the increased investment in heterocyclic-based anti-cancer drug design continue to justify their place in the race to combatting one of the world's most devastating diseases?



**Figure 1**  
The molecular structure of vincristine

### The role of heterocycles in anti-cancer drug design

It is precisely because heterocycles are so prevalent in nature that they have become so important for anti-cancer drug design. Representing an extremely large cohort of molecules with such an unprecedented level of variability in terms of the interactions they can engage with, heterocycle-based compounds not surprisingly have formed the basis of drug therapies time and again. As many enzyme-binding pockets are predisposed to interacting with heterocyclic moieties, heterocycles are a good choice when designing molecules that will interact with targets and disrupt the biological pathways associated with cancer progression. Pathways related to cell growth and development are often targeted by such anti-cancer therapies. Moreover, the relative ease by which heterocyclic rings can be modified with additional substituents allows them to cover a broad area of chemical space, further qualifying them as excellent starting points for anti-cancer drug development.

As a result of these factors, heterocyclic structures have long played a key role in anti-cancer drug design, featuring prominently in anti-cancer drug compounds currently available on the market. Indeed, 65% of the anti-cancer drugs granted market approval by the FDA between 2010 and

2015 contained a heterocycle, and heterocycles form the basis of many of the anti-cancer agents currently in development today.

### Nitrogen-based heterocycles

Nitrogen-based heterocycles are of particular importance in anti-cancer drug design, featuring in almost three-quarters of the heterocyclic anti-cancer agents approved by the FDA between 2010 and 2015. Of all the nitrogen heterocycles, indoles are among the most valuable, with research having demonstrated their ability to induce cell death in a number of cancer cell lines<sup>2</sup>.

Over the last few decades, indole and its derivatives have been shown to modulate a number of biological pathways implicated in the progression of cancer. These include the prevention of cell signalling, normal cell cycle progression, tumour vascularisation and DNA repair, as well as the ability to induce cellular oxidative stress and cell death. Two of the most important early indole-based anti-cancer agents are vincristine and vinblastine – recognised for their tubulin polymerisation inhibition since the early-mid 1960s, and both still of clinical importance today. Vincristine (Figure 1) is used as a combinatorial treatment for acute lymphoblastic leukaemia and both Hodgkin's and non-Hodgkin's lymphoma, whereas vinblastine is

typically used in the treatment of advanced Hodgkin's disease and against testicular cancer. The inhibition of tubulin polymerisation is the mechanism of action of vinblastine, which leads to cell cycle arrest, halting cancer cell division<sup>3</sup>.

Indolocarbazoles are a closely-related derivative of indoles which, much like with the wider remit of heterocycles themselves, exhibit a broad range of activities, and have therefore received significant focus in recent years for their anti-cancer potential. Of particular significance is the proficiency of many indolocarbazoles as protein kinase inhibitors, where constitutively active protein kinases are often key factors in the malignant transformation of cells during cancer initiation.

One such indolocarbazole, the anti-cancer agent midostaurin (an indolocarbazole-based multi-target protein kinase inhibitor), has been approved by the FDA for the treatment of acute myeloid leukaemia as recently as April 2017, which demonstrates just how relevant nitrogen-based heterocycles are for anti-cancer drug design, even to this day.

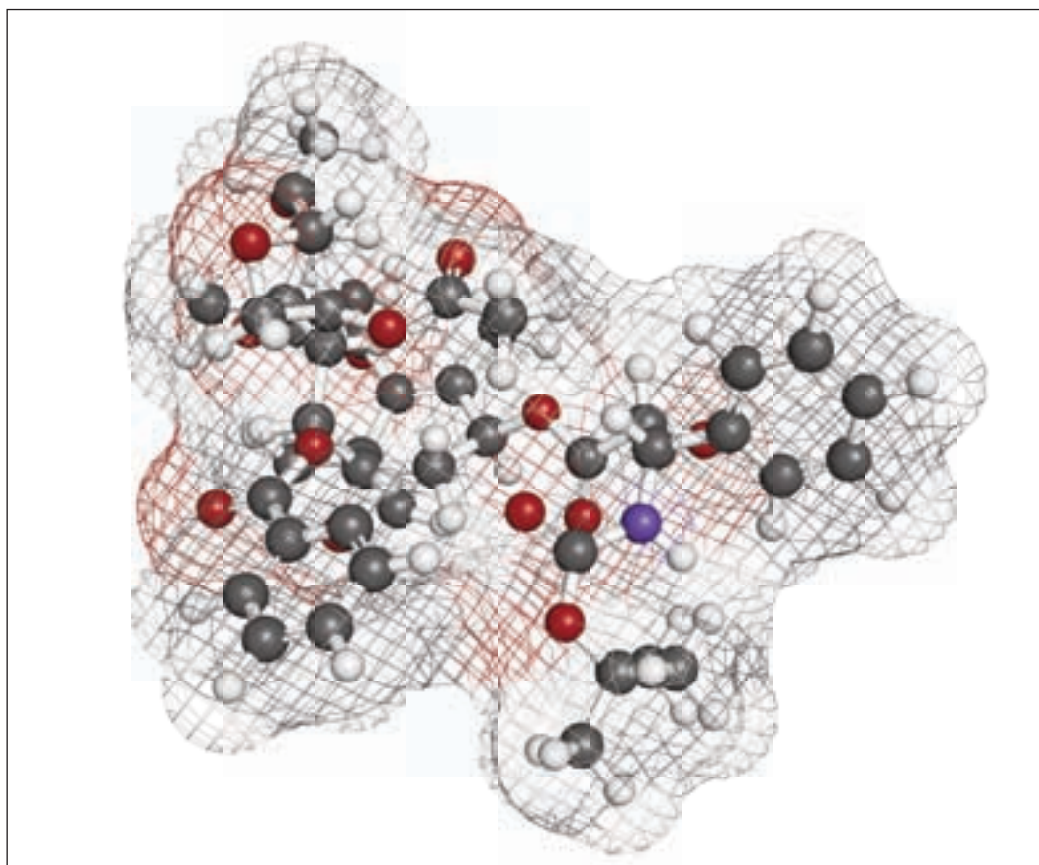
### Oxygen-based heterocycles

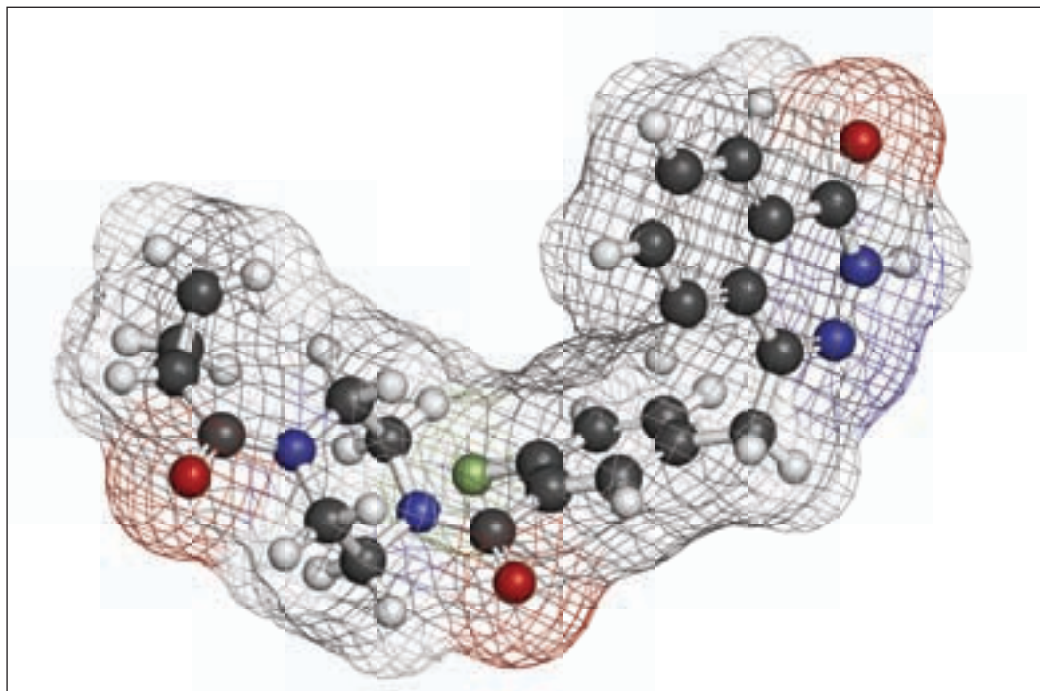
Oxygen-containing heterocycles also feature prominently in many anti-cancer drugs. Among the

earliest to be discovered, paclitaxel is a key drug in cancer therapy. Containing an oxetane ring, its mode of action is based on the depolymerisation of microtubule polymers, resulting in progression inhibition of mitosis in cancer cells. Similar to the mode of action taken by vinblastine, this results in the retardation of cancer cell division, ultimately halting cancer in its tracks. Despite its benefits, however, there are a number of systemic side-effects that have been correlated to the drug, including hypersensitivity, hematological issues and neurotoxicity. As a result, much effort has been devoted to finding alternative therapies that have fewer adverse effects, but still demonstrate the strong therapeutic potential of paclitaxel.

More recently-developed oxygen-containing heterocyclic anti-cancer drugs include microtubule inhibitors cabazitaxel and eribulin, used to treat prostate and metastatic breast cancer respectively. Cabazitaxel (Figure 2) is a tubulin-stabiliser, but is thought to be of particular interest for the treatment of multidrug-resistant tumours owing to its resistance to cellular efflux by the p-glycoprotein efflux pump, expressed by a number of resistance cancer cells<sup>4,5</sup>. Cabazitaxel is also able to cross the blood-brain barrier. Eribulin's mechanism of action

**Figure 2**  
The molecular structure  
of cabazitaxel





**Figure 3**  
The molecular structure of olaparib

on the other hand is somewhat unique, binding only to the growing ends of microtubules during cell division (where other drugs bind both the growing and shortening ends), which leads to prolonged mitotic blockage and ultimately cell death via apoptosis<sup>6</sup>. As mentioned, eribulin is used to treat advanced breast cancer, and is not only effective but exhibits a low level of toxicity compared to alternative cytotoxic agents, making it ideal for patients<sup>7</sup>.

In addition to this, recent research has led to the repurposing of existing oxygen-based heterocyclic drugs originally developed for other disease areas, for use as anti-cancer agents. One notable example is auranofin, a gold-containing heterocyclic compound used historically for the treatment of rheumatic arthritis. Numerous studies are being undertaken to assess auranofin as a therapeutic agent for the treatment of many cancer types, including leukaemia, lymphoma and ovarian cancer (where it recently received FDA approval to undergo Phase II clinical trials). Repurposing drugs in this way is a far more affordable approach to drug discovery, owing to the significant costs associated with novel candidate identification and other research and development activities<sup>8</sup>.

### Sulfur-based heterocycles

Sulfur is a key component in several vitamin co-factors, sugars and nucleic acids, and plays an important role in regulating translation via the sulfuration of transfer RNA. Given the significance of

sulfur in biological systems, sulfur-containing heterocycles have received much attention in the development of anti-cancer drugs, much like their oxygen- and nitrogen-based counterparts. For instance, in a recent screening study, thiophene derivatives were assessed for their antiproliferative activity against human breast adenocarcinoma cells, with a number of compounds found to show promising inhibitory effects. The researchers reported that their findings could provide a basis by which future tyrosine kinase inhibitors may be designed, with fewer side-effects<sup>9</sup>.

In addition, thiadiazole and thiazole structures have also shown to be of importance for cancer research in recent years; with a number of thiazole-based nitrogen mustard heterocycles having recently been shown to exhibit strong inhibitory activity towards a panel of human cancer cell lines. Dabrafenib is a thiazole-containing anti-cancer drug molecule that was approved by the FDA in 2013 for use in patients with cancers associated with the mutated version of the BRAF gene. One such group of patients were those suffering from metastatic melanoma, in which almost half of individuals have been shown to possess the mutated version of BRAF. Initial studies had shown that these patients had had vastly improved clinical outcomes and truly encouraging rates of survival as a result of being treated with dabrafenib<sup>10</sup>.

It is clear from these advances that heterocycles of many different species continue to form the

### References

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basis of a multitude of successful anti-cancer treatments. It is no wonder, therefore, that they continue to be a focus within the drug discovery industry, with drug developers understanding that their vast repertoire of molecular interactions make them fantastic anti-cancer drug candidates.

## Putting heterocycles at the heart of anti-cancer drug discovery

Despite the wide range of heterocyclic anti-cancer drugs currently available on the market, challenges around multi-drug resistance, poor therapeutic efficacy, adverse side-effects and poor bioavailability necessitate the continued development of novel anti-cancer agents. The majority of the drugs available on the market start their drug discovery and development journey as ‘hit’ compounds in a high throughput screening assay.

Take olaparib, for example, a heterocyclic PARP-1 inhibitor that was approved by the FDA in late 2014 for the treatment of ovarian cancer (Figure 3). PARP-1 is the most abundant member of a family of poly ADP ribose polymerase (PARP) enzymes that are implicated in a range of important cellular functions including DNA repair, cell replication and differentiation and necrosis. Several forms of cancer are more dependent on PARP compared to regular cells, including those inclusive of the BRCA mutation, which rely on PARP as a critical DNA repair mechanism. This makes PARP enzymes a particularly attractive drug target in cancer research.

Many PARP inhibitors mimic the nicotinamide structure of the biological molecule nicotinamide adenine dinucleotide (NAD<sup>+</sup>), which is involved in the normal function of PARP-1, in order to interfere with the binding of the substrate to the enzyme’s active site. Olaparib operates in this way, and by preventing cancer cells from undertaking PARP-mediated DNA repair, it is able to stop them from dividing as the cell fails to repair fatal DNA damage. A recent Phase III clinical trial of approximately 300 women with BRCA-related metastatic

breast cancer showed that receiving olaparib reduced the chance of progression of advanced cancer by 42%, with progression itself delayed by approximately three months<sup>11</sup>.

The development of olaparib itself started life from an initial screen of the Maybridge Compound Collection, a library of more than 53,000 hit-like and lead-like compounds. From this screen, the nicotinamide mimic S 15065 was identified as having potential activity against PARP-1. Through systematic structure-activity studies based on chain elongation and substitution of the phenyl ring, the structure of S 15065 was systematically modified and improved in order to maximise the binding ability between the compound and PARP-1. This development process was made significantly easier and faster through the identification of a strong candidate ‘hit’ with desirable binding properties.

## Conclusion

Due to their prevalence in nature as well as their structural and chemical diversity, heterocycles play an immensely important role in anti-cancer drug discovery. Their inclusion in approximately two-thirds of the anticancer drugs approved by the FDA in the first half of this decade highlights their ongoing importance in cancer research, with research demonstrating time and again the central role they have to play in the fight against cancer.

The use of compound screening collections with a strong focus on heterocyclic-based structures can not only lead to the identification of a wide number of potentially successful drug candidates, but can also fast-track the drug development process, ultimately saving time, money and resources. **DDW**

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